



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/445, 9/08</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/25349</b> <b>(43) International Publication Date:</b> 27 May 1999 (27.05.99)
<b>(21) International Application Number:</b> PCT/GB98/03479 <b>(22) International Filing Date:</b> 19 November 1998 (19.11.98) <b>(30) Priority Data:</b> 9724506.2                      19 November 1997 (19.11.97)      GB 9818109.2                      19 August 1998 (19.08.98)        GB <b>(71) Applicant:</b> DARWIN DISCOVERY LIMITED [GB/GB]; Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). <b>(72) Inventor:</b> BROWN, Stephen; Darwin Discovery Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). <b>(74) Agent:</b> GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> ANAESTHETIC FORMULATION  <b>(57) Abstract</b>  <p>A pharmaceutically acceptable aqueous solution which is isobaric or hyperbaric, and isotonic, with respect to cerebrospinal fluid (CSF), comprises a 1-alkyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamide anaesthetic agent such as bupivacaine or levobupivacaine and a saccharide. If the amount of the anaesthetic agent is no more than 0.75 % w/v, a salt or another additional non-saccharide is present. Accordingly, the amount of the saccharide can be kept below that which would provide isotonicity in the absence of the additional non-saccharide.</p>		

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## ANAESTHETIC FORMULATION

### Field of the Invention

This invention relates to a new formulation of long-acting local anaesthetics.

### Background of the Invention

5       A known class of long-acting local anaesthetics comprises 1-alkyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamides. This class includes racemic bupivacaine, levobupivacaine, mepivacaine and ropivacaine. Racemic bupivacaine is widely used, and is available for both epidural and spinal administration.

      The effective utility of levobupivacaine in man, *in vivo*, is evidenced for the first  
10   time in WO-A-9510276, WO-A-9510277 and Gristwood *et al*, Exp. Opin. Invest. Drugs 3(11):1209-12 (1994). The latter documents indicate the potential utility of levobupivacaine in obstetrics, in part at least because of reduced CNS side-effects.

      WO 90/00390 discloses aqueous solutions for spinal analgesia, comprising dezocine, bupivacaine and also 5-10% w/v glucose if it is desired that the solution should  
15   be hyperbaric. The solutions of the Examples which are hyperbaric are also hypertonic.

      Chung *et al*, Br. J. Anaesth. (1996) 77(2):145-9, discloses the use of hyperbaric solutions containing 0.25% w/v bupivacaine and 5% w/v glucose, for spinal anaesthesia. This was done as part of a study to determine the effect of volume of solution administered.

20       Hytta *et al*, Regionale-Anaesthesie (1982) 5:85-8, discloses the use of 0.5% bupivacaine, either "isobaric" (Marcain®) or hyperbaric (8% glucose). The former is presumably plain Marcain® which is in fact hypobaric.

      In the US, a hyperbaric formulation of bupivacaine is available, comprising 2 ml ampoules of 0.75% bupivacaine (racemate) and 8.25% glucose. The use of 0.75%  
25   solutions of racemic bupivacaine is contra-indicated, in obstetrical anaesthesia. The Physician's Desk Reference® carries a "black box" warning.

      In Europe, 4 ml ampoules are available which contain 0.5% bupivacaine and about 8% glucose. These formulations are hypertonic, having an osmolality of approximately 500 mOsm/kg.

30       There are certainly good reasons for including glucose. As reported by Logan *et al*, Brit. J. Anaesthesia (1986) 58:292-296, plain 0.5% bupivacaine has wide variability in terms of its intrathecal spread, when administered for spinal anaesthesia. A hyperbaric

solution containing 8% glucose spreads rapidly but predictably; see Chambers *et al*, Brit. J. Anaesthesia (1981) 53:279-282.

Bannister *et al*, Brit. J. Anaesthesia (1990) 64:232-234, reports the effects of intrathecal injection of 0.5% bupivacaine in solutions containing 0.33%, 0.83% or 8%  
5 glucose. It is suggested that, whereas using 0.33% glucose resulted in variable blocks, as seen using the plain solution, 0.83% glucose is preferable. It is reported that "Making bupivacaine slightly hyperbaric seemed to produce a predictable spinal anaesthetic"; however, formulations comprising 0.5% bupivacaine and 0.83% glucose are in fact hypobaric.

10 It has apparently been accepted by anaesthetists that a high concentration of glucose is necessary. This is despite the fact that such formulations have been associated with neurotoxicity.

#### Summary of the Invention

This invention is based at least in part on the realisation that, in order for a  
15 formulation of bupivacaine to be most useful for spinal administration, i.e. at least isobaric and also isotonic with respect to cerebrospinal fluid (CSF), the level of saccharide should be chosen with relation to the amount of bupivacaine, and should be in a range between those previously suggested. The ability to produce an isotonic formulation means that potential exchange of solutes with the cellular material in CSF  
20 is avoided.

Investigation of various solutions of levobupivacaine, has shown that, at relatively high concentrations and on the addition of glucose, the total amount of the two compounds alone may be sufficient to provide isotonicity. More particularly, at above 0.75%, the level of glucose can be below 5% w/v, while still providing isobaricity or  
25 hyperbaricity. When the concentration of the anaesthetic is lower, the inclusion of an additional non-saccharide compound allows the same combination of parameters to be achieved.

According to the present invention, the beneficial effects of a 1-alkyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamide such as bupivacaine can be provided in  
30 combination with a relatively small amount of glucose and, if necessary, a salt such as NaCl. The glucose provides adequate baricity, whilst the salt makes the composition isotonic. The use of large amounts of glucose is thus avoided, and the risk associated with contact between the composition and plasma or cerebrospinal fluid is reduced.

### Description of the Invention

A solution of the invention will usually be sterile, and typically comprises up to 1% w/v of the anaesthetic, e.g. at least 0.25%, and often 0.5 to 0.75% w/v. An advantage of the use of levobupivacaine over bupivacaine may be the ability to use higher concentrations.

Preferably, a composition of the invention is made up in unit dosages, e.g. of 2 or 3 ml, suitably in a sealed container, e.g. of glass or a transparent plastics material. One preferred formulation comprises 2 ml ampoules or vials of 0.75% levobupivacaine (this compound is described herein for the purposes of illustration only).

Spinal administration may be by any conventional means. The formulation will generally be given to provide anaesthesia and analgesia during surgical procedures and also in Caesarean section and to treat chronic pain.

Levobupivacaine used in the present invention is preferably substantially free of dextrobupivacaine, and is more preferably in at least 90%, and most preferably at least 99%, enantiomeric excess with respect to dextrobupivacaine. Throughout this specification, reference to bupivacaine and its enantiomers includes pharmaceutically-acceptable salts thereof. Such a compound is typically provided as the HCl salt. Any other salt that is present must of course be physiologically-acceptable, and will usually comprise an inorganic cation. For example, it may be an alkali metal salt such as NaCl.

The administration of levobupivacaine over a range of concentrations, including those currently used for the racemic drug and higher concentrations, can be carried out for significantly longer periods than at present, again as a result of the reduced side-effects experienced with levobupivacaine. For instance, levobupivacaine can be administered to a patient safely for at least 24 hours, often up to 72 hours, and even for periods of up to a week or a fortnight, or longer. It can, of course, be administered for similar periods already used for the racemic drug, e.g. between 3 and 6 hours.

The following Examples illustrate the invention. These Examples use levobupivacaine; using bupivacaine instead should have no effect on osmolality or baricity, at equimolar concentrations.

Example 1

Various aqueous formulations of levobupivacaine ("levo") and dextrose were made. They and their baricity and tonicity (and also the corresponding values for CSF) are given in the following Table.

5	Product	Specific Gravity	Osmolality (mOsm/kg)
	CSF	1.0062-1.0082	306
	0.75% Levo + 0 dextrose	1.001	46
10	0.75% Levo + 2.2% dextrose	1.0082	170
	0.75% Levo + 8.25% dextrose	1.029	510
	0.5% Levo + 0 dextrose	1.000	32
15	0.5% Levo + 2.5% dextrose	1.0082	168
	0.5% Levo + 8.25% dextrose	1.028	488

20 Formulations containing more than 2.2% dextrose with 0.75% (7.5 mg/ml) levobupivacaine, or more than 2.5% dextrose with 0.5% (5.0 mg/ml) levobupivacaine, will be technically hyperbaric in all patients. Such formulations, containing less than 5% dextrose, are hypo-osmolar; a suitable salt (NaCl) is added to make the formulations isotonic.

25 Example 2

An aqueous formulation was prepared comprising 0.5% or 0.75% w/v levobupivacaine, 4% w/v dextrose and 0.15% NaCl. This was an isotonic, hyperbaric composition suitable for spinal administration, to provide safe, effective anaesthesia.

30 In summary, it has been shown that it is possible to reduce the level of glucose in the formulation whilst maintaining an appropriate degree of baricity. Also by the addition of physiologically-acceptable inorganic salts such as sodium chloride, an osmotically-balanced formulation which is isotonic with CSF and body fluids (approximating to 300 mOsm/kg) has been achieved.

CLAIMS

1. A pharmaceutically-acceptable aqueous solution which is isobaric or hyperbaric, and isotonic, with respect to cerebrospinal fluid (CSF), and which comprises a 1-alkyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamide anaesthetic agent and a saccharide,  
5 provided that, if the amount of the anaesthetic agent is no more than 0.75% w/v, an additional non-saccharide is present and the amount of the saccharide is below that which would provide isotonicity in the absence of the additional non-saccharide.
2. A solution according to claim 1, which comprises up to 1% w/v of the anaesthetic agent.
- 10 3. A composition according to claim 1 or claim 2, which comprises more than 0.75% w/v of the anaesthetic agent, and the non-saccharide is absent.
4. A composition according to claim 1, which comprises up to 0.75% w/v of the anaesthetic agent.
5. A solution according to claim 4, which comprises 0.5 to 0.75% w/v of the  
15 anaesthetic agent.
6. A solution according to any preceding claim, wherein the saccharide is glucose.
7. A solution according to any preceding claim, which comprises more than 1% w/w of the saccharide.
8. A solution according to claim 7, which comprises more than 2% w/w of the  
20 saccharide.
9. A solution according to any preceding claim, wherein the non-saccharide is present and is a salt comprising an inorganic cation.
10. A solution according to claim 9, wherein the salt is NaCl.
11. A solution according to any preceding claim, which is hyperbaric with respect to  
25 CSF.
12. A solution according to any preceding claim, wherein the alkyl group has 1 to 4 C atoms.
13. A solution according to claim 12, wherein the anaesthetic agent is bupivacaine.
14. A composition according to claim 12, wherein the anaesthetic agent is  
30 levobupivacaine.
15. A container containing a sterile solution according to any preceding claim.

# INTERNATIONAL SEARCH REPORT

I. national Application No

PCT/GB 98/03479

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K31/445 A61K9/08

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 90 00390 A (ASTRA) 25 January 1990  cited in the application  see page 2, line 13 - line 14  see claims 1,2,4-7  see examples  see page 3, line 12 - line 15  see page 3, line 31 - line 32  ---  -/--</p>	1-13

☒ Further documents are listed in the continuation of box C.

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I. International Application No

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

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